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What is the place of peritoneal dialysis in the integrated treatment of renal failure?

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What is the place of peritoneal dialysis in the integrated treatment of renal failure? The role of peritoneal dialysis (PD) in renal replacement therapy (RRT) remains unclear. There are no controlled trials to provide hard evidence of its efficacy. Comparative studies with haemodialysis from different centres and countries have given conflicting results even when allowing for case mix. Data from the United States on patients starting or receiving treatment in the late 1980s suggested a worse prognosis for older patients, particularly diabetics receiving PD as compared to HD. Analysis of the USRDS data base for patients starting in the early 1990s shows an improvement in outcome but with no difference in overall mortality. The Canadian registry has recently published data showing a better survival with PD than with HD in the first two years of RRT. Morbidity is similar with both therapies, although hospitalization is increased with PD. Unfortunately long-term technique survival is not as good with PD. However, PD has certain medical advantages, particularly the maintenance of residual renal function that contributes to solute and fluid removal. It may also postpone the onset of amyloidosis. Patients transplanted after previous PD have a decreased risk of early acute renal failure and equally good long-term results when compared to those patients who were on HD before transplantation. The quality of life is as good with PD as with center HD, and there are social advantages to PD including an increased chance of employment, more flexible holidays and avoidance of thrice weekly travel to a dialysis center. PD also has logistical advantages and can be utilized by the majority of new patients. We therefore conclude that PD has potential advantages early in the course of RRT, and should therefore be offered as a first option to all suitable new patients. Whether PD has a major or minor role in later years (>5) remains unclear.

More than twenty years after its inception as an accepted modality of renal replacement therapy (RRT) the place of peritoneal dialysis (PD) in comparison with hemodialysis (HD) and transplantation remains unclear. From a 40% usage in the UK and New Zealand, its acceptance varies across the world to less than a 6% usage in Japan and Germany. Careful analysis of patient and technique survival rates, however, indicates that over the first five years

of RRT, CAPD is as effective as HD and may even offer certain advantages. We therefore contend that PD should be considered equally with HD and transplantation as modes of RRT, and that each of these therapies should be freely available and used as appropriate by an individual uremic patient during his or her lifetime as part of an integrated package of care.

The aim of RRT should be to restore patients to as normal a level of health as possible and to ensure full social and physical rehabilitation. None of the available therapies offers a cure for renal failure and each has its problems. PD, for instance, can partially replace renal excretory function but clearly does not in any way substitute for the normal endocrine activities of the kidney. The challenge for nephrologists is to use each of the therapies to its greatest advantage and thus to maximize the quality of care and the longevity of RRT.

COMPARISON OF OUTCOME WITH HEMODIALYSIS

The major difficulty in objectively assessing the role of PD is that there is no randomly allocated prospective trial comparing the different therapies. As a result, any comparisons should be treated with caution and should include as detailed analysis of the case mix as possible.

The first serious attempt to look at outcome after correction for confounding variables was made by Burton and Walls [1], who concluded that on an intention to treat basis there was no difference in mortality between PD, HD and transplantation. Subsequently several studies have been published, and some of these are summarized in Table 1 [2–7]. As can be seen, PD has been reported to give better, worse or equal survival to HD, and there are differences even between those reports that use a case mix analysis.

The largest study to date was the USRDS analysis, which looked at 681 PD and 3376 HD patients in 1986 and 1987, and concluded that outcome was worse for diabetic patients aged 58 years or older if they were treated with PD [7]. Lunde et al examined the outcome for 308 PD and 1244 HD individuals aged 65 years or older, who started RRT

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Table 1. Survival comparisons: Hemodialysis versus peritoneal dialysis

Study	Reference	Year	Outcome
Maiorca	[2]	1991	CAPD better in elderly
Piedmont	[3]	1995	No difference
Canada	[4]	1995	CAPD better
Lombardy	[5]	1995	CAPD worse
Australia	[6]	1995	CAPD worse
USRDS	[7]	1994	CAPD worse for elderly diabetics

from 1980 to 1987 inclusive [8]. Although there was a trend to a higher mortality in elderly diabetics receiving CAPD, this was not statistically significant. Using similar methodology Vonesh and Moran recently looked at comparative survival rates for incident HD and PD subjects as recorded by the USRDS for the years 1989 to 1993 and found no difference in the overall death rate [9], although there was a slight increase among female diabetic subjects [10]. These studies suggest that PD results have improved over time in the USA.

One study that caused concern is that of Bloembergen et al [11]. This again used USRDS data but compared prevalent patients on January 1st of 1987, 1988 and 1989 using a Poisson regression model. On average, PD subjects had a 19% higher risk of mortality. This was significant for older patients who were both diabetic [relative risk (RR) = 1.38, $P < 0.001$] and non-diabetic (RR = 1.11, $P < 0.001$). Unfortunately, this report has been interpreted by some commentators to indicate that PD is a second class therapy and therefore avoided if possible. Since only prevalent patients were included, by definition the investigation excluded those who started and stopped RRT within one year. This could bias the results towards HD since individuals who were referred late during the course of their disease tend to receive HD and are known to have a worse outcome [12]. In addition, the subjects were not a single cohort but had been receiving RRT for varying lengths of time. A further criticism is that the case mix analysis only considered diabetes and no other co-morbid factors [13]. Finally, previous studies have generally used a Cox model to analyze the data, making a direct comparison more difficult.

The mortality of patients on PD in the USA has been compared to that of similar patients in other countries. In the CANUSA PD study the mortality rate in the USA centers was nearly twice that in the Canadian ones [14]. Similarly, patients starting RRT in 1986 and 1987 in Lombardy did better than those in the USA [15]. This difference was not explained even when an allowance was made for demographic and comorbid covariates. These studies suggest there are factors affecting mortality on PD in the USA that are not necessarily relevant elsewhere.

Recently a further analysis of the Canadian registry data suggested that for incident patients, after allowing for co-morbid factors, age, sex, ethnicity, etc., the survival with

Table 2. Comparison of hospitalization

Author	Reference	Year	N	Increased with PD
Burton	[21]	1989	227	Yes
Serkes	[22]	1990	657	Only diabetics
William	[23]	1990	58	Yes, elderly
Singh	[24]	1992	40	No
Maiorca	[25]	1993	494	Yes
Habach	[26]	1995	221301	Yes

PD was better in the first two years of treatment compared to HD, with subsequently no difference up to four years [16]. This conclusion was reached using a Poisson regression analysis that accounted for treatment modality switches. In contrast, using a Cox regression model, which is the technique used by most other registries to date, there was no significant difference in outcome between the two types of dialysis on an intention to treat basis. No information on dialysis efficiency, such as, Kt/V values, was provided, so it remains possible—although unlikely—that the HD patients were relatively underdialyzed. One study has suggested that when HD and PD patients receive equivalent amounts of dialysis they have the same outcome [17].

As can be seen from the above, the conclusion reached from examining registry data can be affected by the method of analysis. It should also be noted that because information concerning large numbers of individuals is being assessed, small differences can be statistically significant. For instance, if PD has a RR of 1.1 compared to HD and the mortality rate for the latter is 20% over a certain period of time, this means that for PD the rate will be 22%. The relevance of this difference to the individual patient is unclear, particularly when other issues such as quality of life are taken into consideration. The consensus view is that the differences between the results coming from the various registries are due at least in part to unmeasured variations in case mix, such as the relative severity of different comorbid conditions [18]. The reasonable conclusion from all this information is that mortality is the same for HD and PD when comparing identical types of patients, at least for the first few years of RRT. It should be acknowledged, however, that this conclusion may not have been derived from a comparison with the best possible results. To date the highest rate of survival with HD is apparently that reported by the unit in Tassin [19]. It is not clear how universal their results are, nor whether there was any patient selection in Tassin, but certainly no one has ever claimed as good an outcome with PD.

With respect to morbidity, Maiorca and Cancarini made a detailed survey of the literature and concluded that there was little difference between PD and HD [20]. One indirect marker of morbidity is hospitalization. Table 2 summarizes the more recently published findings [21–26]. It is clear that hospitalization is more likely to be necessary with PD than HD. Burton and Walls noted that the difference decreased

with time, and others have claimed that if episodes of peritonitis are not considered then there is no significant difference [21].

One consideration when offering PD as an effective form of RRT is how long treatment can continue. There is little doubt that technique survival is usually shorter with CAPD than HD. As evidence for this statement it is the fact that there are relatively few patients who have had more than 10 years of continuous treatment with PD as compared to HD. Despite this finding, the Italian cooperative PD study reported a technique survival of 62% at four years and 48% at eight years [27]. Our own data in comparison to HD show no difference in technique survival at four years, but then show an increasing difference in favor of HD up to eight years. One difficulty with analyzing technique survival is that death on PD is regarded as lost to follow up. It is possible that this may give an over-optimistic result, as it could be argued that it does not take account of the fact that death may have been related to inadequate treatment, for example, under-dialysis or fluid overload.

POSSIBLE ADVANTAGES OF PERITONEAL DIALYSIS

There are possible medical advantages to be gained from using PD. It is well recognized that residual renal function (RRF) is better preserved during PD than HD [28]. RRF is of considerable benefit to the dialysis patient. In their long term study, Faller and Lameire demonstrated that the loss of clearance over time in patients on PD was related to the decline in RRF rather than to a decrease in membrane function [29]. Thus, RRF makes a significant contribution to total clearance and to the maintenance of fluid balance. It allows the patient a more liberal diet/fluid intake and may delay the onset of dialysis-related amyloidosis [30], though this has recently been questioned [32]. RRF, rather than peritoneal clearance, both at baseline and over time, is a major factor contributing to survival of PD patients [32]. When the difference in loss of RRF was described, most, if not all, of the HD patients were being treated with cuprophane or other relatively bio-incompatible dialyzers. A recent, small, randomly allocated trial has suggested that the use of a polysulfone membrane is associated with better preservation of RRF as compared to cuprophane [33]. There are no published data comparing whether the decline in the RRF is the same as that which occurs with PD when using polysulfone or a similar membrane. It is also interesting to note that one report has suggested that RRF lasts longer on CAPD than on automated peritoneal dialysis (APD) [34]. If PD is to be successful, efforts clearly need to be made to preserve RRF, such as avoiding nephrotoxic antibiotics [35] and possibly using a loop diuretic. This may not preserve RRF with regards to clearance, but may improve fluid balance. It is noteworthy that in the study of Faller and Lameire, urine volume was greater in the Colmar patients as compared to those

treated in Gent and significantly more patients of the former group were taking a loop diuretic [29].

As with HD, any complication of uremia can occur during PD treatment, though on average PD patients have a higher hemoglobin concentration. Since recombinant erythropoietin is now available this difference has become an economic rather than a medical advantage.

It has been suggested that PD patients may have better cognitive function than those receiving HD. Garcia-Maldonado, Williams and Smith reported that those individuals receiving CAPD had a better mental performance [36]. There was, however, a significantly higher hematocrit (34.4) in the PD group compared with HD subjects (28.4) and it has been shown that treatment of anemia with recombinant human erythropoietin improves cognitive function [37, 38]. Thus, in the absence of a randomly allocated prospective trial or a very large cohort observation in which confounding variables such as comorbidity and hemoglobin concentration can be eliminated, this possible benefit of PD remains unproven.

For many patients the ultimate goal is a successful transplant. Bleyer et al have recently suggested that PD patients may have better outcomes in the first week after cadaveric renal transplantation than do HD patients [39]. In particular, they were less likely to need postoperative dialysis. The authors speculated that this might be due to greater antigenic stimulation during HD. An alternative possibility is that PD subjects are less likely to get postoperative acute renal failure since they are more likely to be well hydrated [30]. Van Loo et al compared transplant outcomes for 117 patients who had previously been on CAPD to 117 individuals who had had prior HD [40]. Delayed graft function requiring dialysis postoperatively occurred in 27 of the PD and 59 of the HD patients ($P < 0.0001$), though there were no differences in mean serum creatinine at six weeks or six months. Similar results have been reported by the Australia and New Zealand Registry (Grabin, personal communication). Maiorca et al, in contrast, found no difference in incidence or length of delayed graft function when comparing the previous type of RRT [41]. Long-term graft survival, however, is the same irrespective of the previous mode of dialysis [41]. It is also claimed that the relatively improved RRF of PD makes it easier to perform the uretero-vesical anastomosis, reducing the chances of leaks, etc., since the bladder will be less contracted. However, there is no detailed analysis of post-transplant urological complications in relation to the previous mode of dialysis. There are also other distinct advantages in proceeding to a graft from PD in contrast to HD [42]. For instance, since PD is a home therapy there is considerably less risk of acquiring a blood borne virus such as hepatitis C. With the advent of erythropoietin, however, the greater risk of antigen sensitization as a result of blood transfusion during HD (because of the lower average hemoglobin) should have disappeared. There remains the

possibility that for highly sensitized individuals PD could have an advantage because there is less risk of inadvertent blood loss requiring a transfusion [42].

The original study by Burton and Walls suggested that after allowing for case mix, survival was equally good on an intention to treat basis irrespective of the mode of RRT, including renal transplantation [1]. This latter finding has recently been challenged by the findings of Edwards, Bennett and Cecka, who looked at the outcome of patients established on the transplant waiting list and thus presumably those with the same relatively low prevalence of co-morbid factors [43]. They compared survival in those who were transplanted to those who remained on dialysis. Although there was an early small increase in mortality after transplantation, within less than one year after the operation survival was better for those with a new kidney as compared to patients remaining on dialysis. This difference occurred even if there were three to six mismatches. This study did not distinguish between PD and HD patients on the waiting list. If confirmed, these results suggest that a transplant is the best RRT in terms of survival. Maiorca et al found that patients on the transplant waiting list had the same survival whatever the type of dialysis being used [41].

QUALITY OF LIFE WITH RENAL REPLACEMENT THERAPY

Since by definition RRT must be life long, it is important to consider not only crude survival but also the quality of life the various therapies offer. Again, there are no randomly allocated controlled trials but there is broad consensus that transplantation gives the best quality of life [44, 45]. This conclusion is justified by the fact that patients act as their own controls and report a substantial improvement after a successful graft. Comparisons of PD with HD must be treated with considerable caution. The studies that are available, however, suggest PD gives an equally good and possibly a better quality of life [46–50]. There are certainly advantages of PD, including the fact that it is a home treatment that avoids repeated visits to the dialysis unit. Holidays and travel are more flexible since the individual is not confined to certain geographical areas where there is a renal unit. CAPD potentially allows the patients to have more control over their own lives and should provide more chance of rehabilitation [42]. There are reports suggesting that individuals receiving PD are more likely to be employed than with HD [51, 52]. Woods et al reported that patients trained to do self-care HD at home or in a center had a significantly lower mortality than those cared for by professional staff, even when factors such as comorbidity were included in the analysis [53]. This suggests that some form of home treatment should be encouraged and clearly PD is ideal in this respect. Unfortunately, as noted above, no such clear advantage in terms of survival has been reported for PD in comparison with center HD. The better result with self-care HD may be due to a selection bias in

choosing patients for this type of RRT, which includes psychological factors such as compliance, mental stability and intelligence. No analysis to date has been able to assess these variables.

De Vecchi et al have published an interesting survey of 120 patients who had experienced both PD and HD for at least six months with transfers in either direction [54]. Since the usual reason for a change was a problem occurring with the initial therapy, most subjects preferred their current treatment at the time of asking. There were no marked differences overall between the two therapies when the reasons for their preference were assessed. One further way of assessing the impact of RRT is to assess the illness intrusiveness, which measures the degree to which the illness interferes with lifestyle, activities and interests [55]. When the three types of RRT were compared, only renal transplantation had significantly less impact. There were no differences between the various types of dialysis [55]. Though PD is theoretically a self-supervised treatment, in practice a carer is often involved. A small study in Cardiff found that the caregivers of home HD patients found the actual therapy stressful, but those involved with PD subjects thought the treatment was time consuming and tedious (Salek, personal communication). Maiorca commented that after a number of years there may be burn out of either the patient and/or caregiver [56]. As patients age, there may come a point in time when he or she is no longer able to do this procedure.

LOGISTICAL ADVANTAGES OF PERITONEAL DIALYSIS

There are a number of logistical advantages of PD. Since all health care systems are under financial pressure, PD does allow expansion with limited resources and avoids a major capital program [42]. This policy occurred by default in the UK during the 1980s. PD certainly requires a lower staff:patient ratio than center HD, and standard CAPD is cheaper. It is not yet clear whether measures designed to improve adequacy, such as APD with its daytime bags, have a cost advantage, at least over self-care HD.

FACTORS INFLUENCING THE CHOICE OF PERITONEAL DIALYSIS

One further consideration is whether there are any medical reasons for strongly recommending HD or PD. Hamburger et al have published a suggested list showing that the large majority of patients can be considered for PD [57]. For some individuals PD is clearly preferred. These include those with problems with vascular access, small children, those who live a long distance from the dialysis center, those with complications from HD, and those with a strong desire for independence and autonomy. It can also been argued that in the absence of a live-related kidney transplant donor, it is preferable to begin RRT with PD

since in addition to all the possible advantages noted previously, it may delay the use of blood access sites.

One factor that influences whether or not a patient is treated by PD is the time of referral. Patients referred early in their disease to a renal unit are more likely to choose PD. Those who are referred late, particularly if they need emergency dialysis, usually opt to stay on HD [58, 59].

Despite all the reasons given above, the use of PD varies widely throughout the world. Nissenson et al have given a cogent review of the non-medical factors that impact on RRT selection, and clearly imply that in some centers the patients are denied an effective form of therapy [60].

ROLE OF PERITONEAL DIALYSIS IN RENAL REPLACEMENT THERAPY

In view of the evidence it is reasonable to conclude that PD is equally as good, if not better than HD, as an initial form of RRT and is acceptable to many patients. Furthermore, reviewing the literature it is reasonable to draw the conclusion that if medically suitable, PD should be the first option for RRT (in the absence of a suitable live donor) when a patient reaches end-stage renal failure. The benefits as noted previously include preservation of RRF, a possible delay in the onset of amyloidosis, better early survival, reduced risk of being infected by a blood borne virus and better short-term results with a transplant. One could thus argue that all medically suitable patients should be encouraged (but not coerced) to start with PD. This suggestion is made because Szabo et al have shown that when freedom of choice was withdrawn, the patients' quality of life as judged by mental scores became significantly worse [61], though no changes were seen in physical scales. We therefore suggest a schema for managing patients with end-stage renal disease that is depicted in Figure 1.

As a result of the foregoing analysis, one is led to a number of propositions: (1) patients should have a free choice, assuming the appropriate resources are available; (2) physicians should offer all three types of RRT; (3) it is likely that each form of therapy may have a role to play during the lifetime of patients with renal failure. Furthermore, one should no longer be attempting to prove that one form of dialysis is better than another, but rather identify ways in which the differing modalities complement each other. In this respect it is interesting to note the recent report by Van Biesen et al suggesting that patients starting on PD and then switched to HD had better survival than those remaining on their initial treatment of either type [62].

There still remains, however, the unsolved question of whether PD can be used by the majority of subjects after several years of RRT. Foley et al have suggested that during the first two years of RRT there is no difference in mortality comparing PD to HD, but subsequently it is increased in PD patients [63]. The answer will almost certainly depend on how easy it will be in practice to

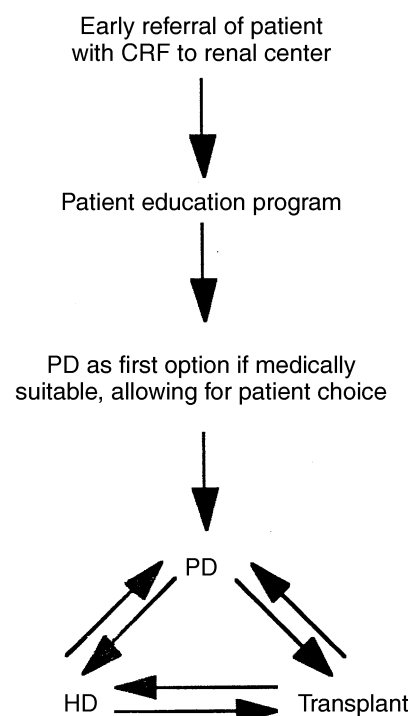


Fig. 1. Suggested schema for managing new patients with end-stage renal failure.

augment solute clearance and fluid removal (to replace RRF) without adversely affecting the patients' quality of life. It is worth noting the report of McComb et al [64], who found no improvement in quality of life when patients were switched from CAPD to APD, and thankfully there was no decline either.

One can therefore conclude that PD should be freely available as part of an integrated RRT program. PD is a clear option for the majority of patients needing RRT early in the course of their disease. PD should be an option for increasing numbers of patients after five years or more of RRT, but the size of such a population remains yet uncertain.

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